thereby [illegible] the neural stem cell into the ventral neur[illegible]-
-

--1. Amended. The method of claim 1, wherein the nucleic acid introduction into the neural stem cell incorporates into the chromosomal DNA of the stem cell.--

REMARKS

Claims 1-4 are pending and under examination in the instant application. Applicants have amended claims 1 and 2. Support for these amendments may be found inter alia in the specification as follows: claims 1-2: page 2, line 7; and page 3, lines 11-12. In making these amendments, applicants do not concede the correctness of the Examiner's rejections in the December 4, 2002 Office Action. Applicants maintain that these amendments raise no issue of new matter, and respectfully request entry of this Amendment. Upon entry of this Amendment, claims 1-4 will still be pending and under examination.

Pursuant to 37 C.F.R. §1.121 c 1) (ii), applicants attach hereto as **Exhibit A** a version of the amended claims marked up to show the changes relative to the previous version thereof.

In view of the amendments to the claims and the arguments set forth below, applicants maintain that the Examiner's rejections made in the December 4, 2002 Office Action have been overcome and respectfully request that the Examiner reconsider and withdraw same.

Rejection Under 35 U.S.C. §112, First Paragraph

The Examiner rejected claims 1-4 under 35 U.S.C. §112, first paragraph, for allegedly containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The Examiner stated that the claims are directed to a method of converting a stem cell to a ventral neuron. The Examiner stated that the claims cover in vivo and in vitro applications of the claimed method.

The Examiner stated that the specification fails to provide an enabling disclosure for the claimed method because the specification does not offer specific guidance with regard to the type of stem cell that can be used to produce a ventral neuron using the method as claimed. The Examiner stated that the claims cover the use of any type of stem cell to produce a ventral neuron upon introducing a nucleic acid encoding the Nkx6.1 homeodomain transcription factor. However, the Examiner stated that the specification does not offer any guidance with regard to which type of stem cells could be used to produce a ventral neuron, nor does it provide culture conditions that would be suitable for inducing a stem cell to differentiate into a ventral neuron. For example, the Examiner stated that there is no teaching in the specification for using a hematopoietic stem cell in the claimed method. The Examiner stated that there is no teaching of specific culture conditions that would permit a hematopoietic stem cell to differentiate into a ventral neuron. The Examiner stated that the

state of the art is such that methods of providing a particular type of stem cell to differentiate into a particular type of differentiated cell are not developed by routine experimentation. Furthermore, the Examiner stated that different types of stem cells have differing potentialities in terms of the types of cells they are capable of differentiating into (citing pp. 1-9 of Stem Cells: Scientific Progress and Future Research Directions, June 2001).

In response, applicants respectfully traverse the Examiner's above rejection. Nevertheless, applicants without conceding the correctness of the Examiner's position but to expedite prosecution of the subject application have hereinabove amended claims 1 and 2. Newly amended claims 1 and 2 now recite, in relevant part: "**neural** stem cell" [emphasis added]. Applicants contend that these amendments obviate the above rejection and respectfully request that the Examiner reconsider and withdraw this ground of rejection.

The Examiner also stated that the specification fails to provide an enabling disclosure for in vivo applications of the claimed method because the specification does not provide specific guidance for practicing the claimed invention in vivo. Furthermore, the Examiner stated that the specification does not assert a utility for practicing the claimed method in vivo, and the only potential utility for producing neurons in vivo is for therapy. The Examiner stated that if practiced in vivo, the claimed method encompasses gene therapy. However, the Examiner stated that the specification fails to provide an enabling disclosure for the claimed method because the specification does not enable gene therapy. The Examiner stated that the specification does not teach how to use the claimed methods in gene therapy applications, for the following

reasons.

The Examiner states that the claims involve the introduction of a nucleic acid encoding a transcription factor protein into a stem cell. Thus, the Examiner stated that the claims clearly cover methods of gene therapy. However, the Examiner stated that gene therapy is not routinely successful. Therefore, the disclosure must enable the full scope of the claimed methods with specific guidance. However, the Examiner stated that the specification fails to teach any method for introducing a nucleic acid encoding the Nkx6.1 transcription factor into a stem cell residing in vivo and expressing that gene at a level sufficient to produce ventral neurons and thereby achieve a therapeutic effect in a diseased immunocompetent animal. The Examiner stated that the specification does not provide any guidance as to the level of gene expression required, the type of gene transfer vector to be used, the number of transduced cells needed, the route and time course of administration, when, where, or for how long the therapeutic gene should be expressed, the frequency of administration of the gene therapy vector, or the intended target tissue, for treatment of any pathological condition in an immunocompetent animal. The Examiner stated that the specification also lacks any working examples showing that the contemplated nucleic acid, once delivered to the appropriate site, would be expressed at a level sufficient to provide adequate product to effect a therapeutic result in an immunocompetent animal. The Examiner stated that at the time the application was filed, the art of administering any type of genetic expression vector to an individual so as to provide a tangible therapeutic benefit was poorly developed and unpredictable. The Examiner stated that the NIH ad hoc committee to assess the current

status and promise of gene therapy reported in December 1995 that "clinical efficacy has not been definitively demonstrated at this time in any gene therapy protocol, despite anecdotal claims...," and that "significant problems remain in all basic aspects of gene therapy" (Orkin and Motulsky, p. 1). The Examiner stated that in a review article published in Scientific American in June 1997, Theodore Friedman discusses the technical barriers which have so far prevented successful gene therapy, and states "So far, however, no approach has definitively improved the health of a single one of the more than 2,100 patients who have enrolled in gene therapy trials worldwide" (p. 96). The Examiner stated that in a review article published in Nature in September 1997, Inder Verma states "Although more than 200 clinical trials are currently underway worldwide, with hundreds of patients enrolled, there is still no single outcome that we can point to as a success story" (p. 239). The Examiner stated that the instant specification does not adequately teach one skilled in the art how to use the claimed methods for in vivo gene therapy. Moreover, the Examiner stated that the instant specification does not assert any other use for practicing the claimed method in vivo. Thus, the Examiner stated that absent any showing that the claimed methods can be used in gene therapy applications to produce a therapeutic effect in an immunocompetent animal, such as a human, claims covering gene therapy are not enabled by the disclosure.

In response, applicants respectfully traverse the Examiner's above rejection. Contrary to the Examiner's assertions, the specification provides sufficient description to enable one of skill in the art to make and use the claimed invention without undue experimentation (emphasis added). For example, applicants describe that the method

of claim 1 can be practiced using transfection or transduction - see page 13, lines 14-19 . Transduction and transfection are methods commonly used by those of skill in the art to introduce nucleic acids into cells, whether in vivo or in vitro. Therefore, based on applicants description, one of skill in the art would be able to practice the subject invention without undue experimentation. Accordingly, applicants maintain that the description in the subject application, as described hereinabove, clearly enables the pending claims.

Applicants contend that these remarks obviate the above rejection and respectfully request that the Examiner reconsider and withdraw this ground of rejection.

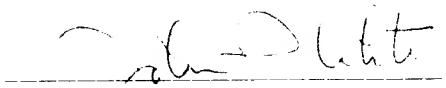
Summary

In view of the amendments and remarks made herein, applicants maintain that the claims pending in this application are in condition for allowance. Accordingly, allowance is respectfully requested.

If a telephone interview would be of assistance in advancing prosecution of the subject application, applicants' undersigned attorney invites the Examiner to telephone him at the number provided below.

No fee is deemed necessary in connection with the filing of this Amendment. However, if any fee is required, authorization is hereby given to charge the amount to Deposit Account No. 19-3125.

Respectfully submitted,



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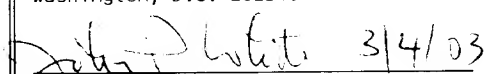
I hereby certify that this correspondence is being deposited this date with the U.S. Postal Service with sufficient postage as first class mail in an envelope addressed to: Assistant Commissioner for Patents, Washington, D.C. 20231.



3/4/03
John P. White Date
Reg. No. 28,678

Marked-up Version Of Amended Claims:

--1. Amended A method of converting a neural stem cell into a ventral neuron which comprises introducing into the neural stem cell a nucleic acid which expresses homeodomain transcription factor Nkx2.1 protein in the stem cell so as to thereby convert the neural stem cell into the ventral neuron.--

--2. Amended The method of claim 1, wherein the nucleic acid introduced into the neural stem cell incorporates into the chromosomal DNA of the stem cell.--